ABSTRACT:

Title: To study the effect of Fasudil on the contractility of isolated non-pregnant human myometrium and to analyse the possible mechanism involved

Background: Preterm delivery is one of the leading causes of perinatal mortality. Current therapy does not confer benefits in reducing perinatal mortality. Septic abortions are induced by RhoKinase activation. Fasudil, Rho-Kinase inhibitor used for cerebral vasospasm is hypothesized to cause relaxation of uterus during preterm labour. We have evaluated the effect of Fasudil on the contractility of isolated non-pregnant human myometrium.

Aim: To evaluate the effect of Fasudil on the contractility of isolated non-pregnant human myometrium and to identify possible mechanisms involved.

Methods: 5 doses of Fasudil were used to evaluate the dose response relationship on the 55 mM KCl-induced contraction of the non-pregnant human myometrium. Effect of 8µM Fasudil was reversed using 3 reversal agents; ODQ (oxadiazolo-quinoxalin-1-one)- a specific guanylyl cyclase inhibitor, L-NAME (L-N Arginine Methyl Ester)- a nitric oxide synthase inhibitor, Di-adenosine Penta phosphate- a specific P2X receptor agonist. The above procedure was evaluated on isolated strips of myometrium obtained from patients undergoing elective hysterectomy using a student's Physiograph (n=13).

Statistical Analysis: Descriptive statistics Mean (S.E.M.), Median (I.Q.R.) are calculated. Wilcoxon signed rank test is used to compare the non-parametric paired data of % effect of Fasudil on KCl induced contraction, both in presence and absence of reversal agents.

Results: Both AUCC and Height of the contraction curve were measured. Fasudil exhibited a significant relaxation on KCl induced contractions at 3 different doses; 4μM, 8μM and 16μM ($p < 0.05$). There was a significant reversal of Fasudil induced relaxation, with all 3 reversal agents; ODQ, L-NAME, DAPP ($p<0.05$).

Conclusion: Fasudil effectively relaxed human myometrium by inhibiting RhoKinase enzyme. RhoKinase induced contraction is likely to involve Nitric oxide downregulation, phosphodiesterase activation and purinergic receptor agonism. By inhibiting RhoKinase one can achieve smooth muscle relaxation involving several parallel mechanisms making Fasudil a good candidate to be evaluated as a tocolytic agent.

Keywords: Fasudil, RhoKinase, Myometrium, Nitric oxide, P2X receptor, cGMP, Preterm labour, Tocolysis.